

REMARKS

Claims 12-15 and 17-19 are all the claims pending in the application. Of these, claims 12-15 and 17-19 are under examination. Claim 16 is withdrawn from consideration as being drawn to a non-elected invention, but may be eligible for rejoinder after the allowance of independent claim 12.

I. The Claims Are Definite Under 35 U.S.C. § 112, Second Paragraph

Claims 12-15 and 17-19 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner contends that the claims are unclear since they do not specify the structural features, including the shape of the carrier or spatial relationships between the various elements.

The 35 U.S.C. §112, second paragraph test of definiteness is whether the claim language reasonably apprises persons skilled in the art of the metes and bounds of the claimed subject matter. See MPEP 2173.02.

Amended Claim 12 recites "A carrier for cell culture in the form of a sheet, comprising: a water-containing gel comprising alginate, wherein a surface of the water-containing gel is coated with collagen to create a collagen layer, and wherein the collagen layer is bound to the surface of the water-containing gel by means of chitosan; wherein the chitosan is formed from a 1-5% aqueous solution." Applicants point the Examiner to the geometric and spatial limits in original Claim 12, including a carrier, a surface and a layer, which define the invention with a reasonable degree of particularity and distinctness. However, to advance prosecution Claim 12 is currently amended, adding even more geometric and spatial indicia. Claim 12 as amended complies with the definiteness requirement of section 112, Claims 13-15 and 17-19 depending from amended Claim 12 also comply with the definiteness requirement of the statute.

Accordingly, withdrawal of this rejection is kindly requested.

II. The Claims Are Patentable Under 35 U.S.C. §103(a)

At pages 3-8 of the Office Action, claims 12-15 and 17-19 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Hara et al (U.S. Patent 6.821.107) in view of Huguet & Dellacherie, and Clapper et al (U.S. Patent 5.512.474).

In order for the Examiner to maintain a rejection under 35 U.S.C. §103, the Examiner must show (1) that the cited references teach each and every element of the claim, (2) that there is a suggestion or motivation in the cited references or the general knowledge of the art to modify the references to make the claimed invention, and (3) that there is a reasonable expectation of success that the modification will yield the claimed subject matter. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See also MPEP §2142. A rejection under 35 U.S.C. §103 may be traversed by showing that the Examiner has not established one or more of the elements of a *prima facie* showing of obviousness. Alternatively, or in addition, a *prima facie* case of obviousness may be rebutted by a showing of unexpectedly superior properties of the claimed invention compared to the closest prior art which is commensurate with the claims. MPEP §716.02(b).

As set forth in the Office Action, the Examiner contends that Hara et al. teach a carrier for cell culture comprising an alginate gel layer formed on a porous membrane, and having an extracellular matrix component layer (collagen). The Examiner admits that Hara et al. do not teach a carrier for cell culture where the collagen layer is bound to a surface of the water-containing gel by means of chitosan as an intermediate layer. However, the Examiner contends that Huguet et al. teach a microcapsule suitable for encapsulation of biological materials including cells. The Examiner contends that the microcapsules of Huguet comprise calcium alginate beads that are coated with chitosan as an outermost layer to study the rate of release of biological materials from the encapsulated beads. In addition, the Examiner contends that Clapper et al. teach a cell culture system comprising a support material for anchorage-dependent cell culture, which comprises a stable combination of a positively-charged molecule, such as chitosan, and a cell adhesion factor such as collagen.

This rejection should be withdrawn, as the cited references fail to render obvious the cell carrier of the present invention. Applicants point out that Huguet et al. do not explicitly teach coating calcium alginate with chitosan in order to provide combined strength and transparency to the water-containing gel layer. Huguet et al. state that their study was conducted to understand the effects of chitosan on the conformation, chemical composition and molecular weight of released compounds. See Huguet et al., page 746, first full paragraph. In fact, Huguet et al. do not suggest, encourage or mention combined bead integrity and visibility vis-à-vis chitosan coating. The Examiner's remarks appear contradictory in that the Examiner contends that chitosan is necessarily transparent (and thus any carrier having chitosan would have the property of being transparent), and then contends that the claims are not limited by the transparent feature, despite the fact that the claims recite the chitosan component. Since Huguet et al. fail to teach or suggest the properties of the present invention, a prima facie case of obviousness has not been established.

In addition, Claim 12 as amended recites "a carrier for cell culture in the form of a sheet, comprising: a water-containing gel comprising alginic acid, wherein a surface of the water-containing gel is coated with collagen to create a collagen layer, and wherein the collagen layer is bound to the surface of the water-containing gel by means of chitosan; wherein the chitosan is formed from a 1-5% aqueous solution." Claim 12 as amended further distinguishes the invention from the art.

Even if a prima facie case of obviousness could be established based on Hara et al., Huguet & Dellacherie, and Clapper et al., which it cannot, the carrier for cell culture of the present invention provides unexpectedly superior results which rebut any prima facie case of obviousness and further support the patentability of the present invention. Applicants have demonstrated in the specification as filed that the claimed sheet carrier for cell culture is unexpectedly superior to the carrier of Hara et al., because the claimed carrier allows for better observation of cells during culture. See specification, page 31 and Table 2, page 28. Table 2 clearly shows that the alginic acid gel membrane modified with chitosan (samples 102 and 103) provides superior visibility (bull's eye symbol, column 7 rows 3 & 4) as compared to the

visibility of sample 101 which does not contain chitosan (open triangle, column 7 row 1). However, Applicants see no indication that the Examiner properly considered Applicants' evidence of unexpectedly superior properties. In accordance with MPEP §2141(III), the Examiner should consider whether the evidence is sufficient to show that the asserted properties (i.e. the combination of both superior strength and transparency) are unexpected over the teachings of the references, and hence sufficient to rebut any prima facie case of obviousness. The Examiner's comments, however, are not supported by such an analysis.

In addition, Dr. Tsuzuki has conducted comparative experiments wherein an alginic acid gel membrane was used to prepare test cell carrier samples. See the attached Declaration of Hirohiko Tsuzuki, at page 2. Some of the carrier samples included chitosan (i.e., sample 203), whereas others did not (i.e., samples 502-503). Dr. Tsuzuki evaluated all samples based upon their varying degrees of strength and transparency. Declaration, page 2.

The results of Dr. Tsuzuki's experiments indicate that the chitosan treated sample, 203, had a superior combination of strength and transparency as compared directly to samples prepared without chitosan (502-503). Declaration, page 3. Applicants observe that chitosan is unique for sheet preparation, as chitosan adds strength to the sheet yet retains transparency, thereby permitting direct cell observation in the present invention. In regard to the Examiner's allegation that transparency is an inherent property of chitosan, the thickness of the chitosan layer is very important to satisfactorily achieve the desired transparency, and a higher thickness of chitosan will reduce the transparency of the chitosan layer. If a chitosan layer is applied to calcium alginate beads, the resulting coating of chitosan will have a higher thickness so that transparency will be reduced or destroyed. Further, if the chitosan layer is too thin, sufficient strength of the claimed carrier is not obtained, and therefore, a concentration of chitosan for the preparation of the claimed carrier is very important to achieve the desired strength and transparency of the claimed carrier. According to Dr. Tsuzuki, only chitosan achieves the desired advantageous effects of the claimed invention. Dr. Tsuzuki's experimental observations provide direct evidence of unexpectedly superior properties, and hence sufficient evidence to rebut any prima facie case of obviousness, had one been properly established at the outset.

In view of the above, withdrawal of the §103 rejection is kindly requested.

III. Double Patenting

At page 8 of the Office Action, claims 12-15 and 17-19 are rejected for obviousness-type double patenting as being unpatentable over claims 1-6 of U. S. Patent No. 7,022,523.

Applicants herewith file a Terminal Disclaimer to obviate this rejection.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



William J. Simmons
Registration No. 59,887

SUGHRUE MION, P.L.C.
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE

23373

CONTROLLER NUMBER